PREPARATION OF 6-STYRYLPHENANTHRIDINES

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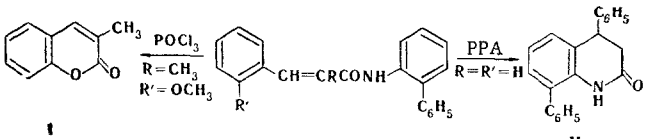
(6-Phenanthridinylmethyl)magnesium halides do not react with aromatic and aliphatic aromatic ketones but do react with aromatic aldehydes to give the corresponding carbinols. The latter are readily dehydrated to the corresponding 6-styrylphenanthridines. 6-Cyanomethylphenanthridine reacts with aromatic aldehydes in the presence of sodium ethoxide to give 6-(α-cyanostyryl)phenanthridines and is converted to 5-acyl-6-cyanomethylene-5,6-dihydrophenanthridine on heating with acetic anhydride or benzoyl chloride.

In connection with an investigation of phenanthridine derivatives containing conjugated groupings, it seemed of interest to establish to what extent substitution of the double bond of 6-styrylphenanthridines affects their physicochemical properties. In the present paper we report attempts to synthesize compounds of this sort, inasmuch as only a few double-bond-unsubstituted styrylphenanthridines are described in the literature. Most of the reported compounds were obtained by condensation of 6-methylphenanthridine with benzaldehyde or its derivatives in the presence of zinc chloride [1, 2]. We used this method to obtain 6-(p-methoxystyryl)phenanthridine in good yield. We also obtained it and 6-styryl-and 6-(p-nitrostyryl)-phenanthridines by condensation of 6-methylphenanthridine with aldehydes in acetic anhydride. However, the indicated methods proved to be unsuitable for the preparation of styryls with substituted double bonds: 6-methylphenanthridine does not react with aliphatic aromatic ketones, while 6-alkylphenanthridines do not react with aldehydes. In order to obtain an α-methyl-substituted styryl, we attempted to cyclize o-methoxy-α-methylcinnamic acid 2-diphenylylamide by the method in [3]. However, treatment of the latter with phosphorus oxychloride gave 3-methylcoumarin (I) instead of the corresponding styryl. There was also partial dealkylation of the methoxy group and formation of 3-methylcoumarin in the preparation of o-methoxy-α-methylcinnamoyl chloride. The cyclization of cinnamic acid diphenylylamides apparently holds little promise for the preparation of styryls, inasmuch as 6-styrylphenanthridine is formed in very low yield also in polyphosphoric acid (PPA), and the chief product is 3,4-dihydro-4,8-diphenylquinolone (II) [4].



I II

In this connection, we attempted to synthesize 6-styrylphenanthridines by dehydration of the appropriate alcohols. It seemed possible to obtain alcohols of this sort (IV, V) by reaction of (6-phenanthridinylmethyl)magnesium halides (IIa, b) with aryl carbonyl compounds. We were able to synthesize IIIa from 6-chloromethylphenanthridine or by the convoy method with dibromoethane. It was found to be more convenient to obtain IIIb by reaction of 6-methylphenanthridine with isopropylmagnesium bromide, as in the method described for quinaldine [5]. Compounds III reacted with benzaldehyde and o-methoxybenzaldehyde to give the corresponding carbinols (IV, V), which were readily dehydrated to olefins (VI, VII). However, IIIb, in contrast to the analogous compounds of α-picoline and quinaldine [5], did not react with ketones in any of the investigated solvents [ether, tetrahydrofuran (THF), dioxane, anisole, and hexamethylphosphoric triamide (hexametapol)]. Replacement of magnesium by lithium also did not give positive results.

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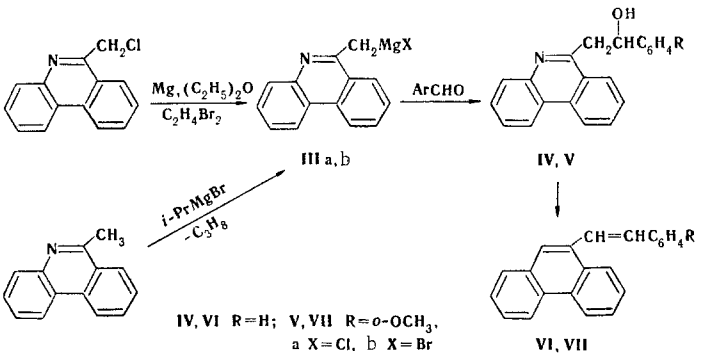
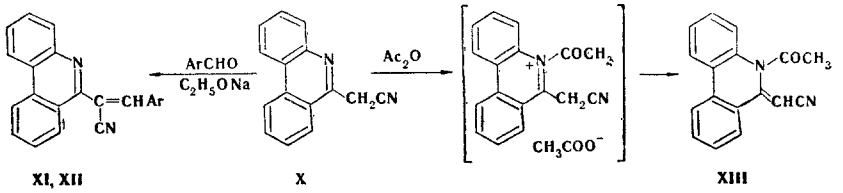


The lack of reaction of IIIb with ketones is apparently due to the greater stabilization and, consequently, lower activity of the 6-phenanthridinyl anion as compared with the analogous anions from α-picoline and quinaldine as a consequence of the higher positive charge in the 6-position of phenanthridine [6, 7]. Considering this, it might have been assumed that 6-formylphenanthridine (VIII) has a high reactivity. However, it did not react with either α-phenylethylmagnesium bromide or even with the much more active ethylmagnesium bromide. In addition, aldehyde VIII did not react in the presence of bases with benzyl cyanide – the usual reaction for aromatic aldehydes. The reason for this low reactivity of 6-formylphenanthridine is not clear, although it may be due in part to the steric effect of the hydrogen in the 7-position. In order to reduce the effect of steric factors and simultaneously activate the methylene group, we subjected 6-cyanomethylphenanthridine (X) to condensation with aromatic aldehydes. This compound proved to be quite active. The corresponding α-cyanostyryl derivatives (XI, XII) were obtained in alcohol media in the presence of sodium ethoxide with benzaldehyde and p-dimethylaminobenzaldehyde. Condensation also occurs with p-nitrobenzaldehyde but is apparently accompanied by side processes that hinder the isolation of the styryl.

An absorption band at ~340 nm, which is shifted bathochromically under the influence of p-nitro and p-methoxy groups, is characteristic for double-bond-unsubstituted phenanthridine styryls. A bathochromic shift of 30-50 nm occurs in acidic media. The presence of a nitrile group in the α-position leads to overlapping of the short-wave and long-wave absorption bands of XI (Fig. 1). This overlapping does not occur in the case of p-dimethylamino derivative XII because of a pronounced bathochromic shift of the long-wave band (Fig. 2). Its color is shifted bathochromically at pH 1 because of protonation of the nitrogen atom of phenanthridine. In strongly acidic media a proton also adds to the nitrogen atom of the dimethylamino group, inducing an increase in the coloration (Fig. 2).

When X was heated in acetic anhydride it reacted with p-dimethylaminobenzaldehyde to give styryl XII. However, the same compound (XIII), which was yellow, was isolated in experiments with benzaldehyde and p-nitrobenzaldehyde. However, XIII was also formed when X was refluxed in acetic anhydride in the absence of aldehydes. This compound does not display either acidic or basic properites. Its IR spectrum contains bands of the stretching vibrations of amide and CN groups. The electronic spectrum of XIII differs from the spectra of phenanthridine and 6-styrylphenanthridine derivatives with respect to the intense absorption band at ~400 nm (Fig. 1). A singlet of an acetyl group appears in the PMR spectrum at ~2.6 ppm. 6-Methylphenanthridine was obtained in high yield as a result of acid hydrolysis of XIII, and 6-cyanomethylphenanthridine was detected as an intermediate by TLC.



XI, XII X XIII

XI Ar=C_6H_5; XII Ar=$C_6H_4N(CH_3)_2$-p

On the basis of these results and the results of a determination of the composition and molecular weight, we feel that XIII is 5-acetyl-6-cyanomethyl-5,6-dihydrophenanthridine. Compound XIII is apparently formed as a result of detachment of a proton from the cyanomethyl group of the initially formed 5-acetyl-6-cyanomethylphenanthridinium salt.

Compound XIII is relatively inert: it is not changed by the action of 2 M alkali at room temperature, does not add hydrogen under normal conditions in the presence of Raney nickel, and does not react on heat-

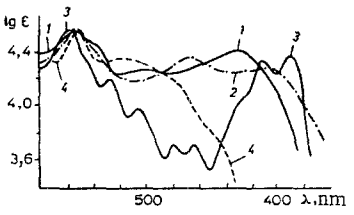


Fig. 1

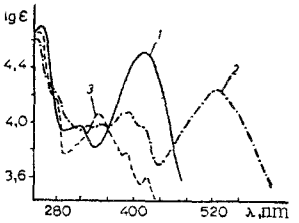


Fig. 2

Fig. 1. UV spectra of phenanthridine derivatives in alcohol: 1) 6-(p-nitrostyryl)phenanthridine; 2) 6-(p-nitrostyryl)phenanthridine at pH 1; 3) 5-acetyl-6-cyanomethylene-5,6-dihydrophenanthridine (XIII); 4) 6-(α-cyanostyryl)phenanthridine (XI).

Fig. 2. Absorption spectra of alcohol solutions of 6-(α-cyano-p-dimethylaminostyryl)phenanthridine (XII): 1) neutral solution; 2) pH 1; 3) pH < 0 (the log D+4.5 values are indicated in place of log ε).

ing with benzaldehyde and its derivatives. However, when it is heated with p-dimethylaminobenzaldehyde in acetic acid it is converted to 6-(α-cyano-p-dimethylaminostyryl)phenanthridine. A compound similar to XIII was also obtained by reaction of X with benzoyl chloride [8].

It is interesting to note that compounds of the XIII type are also apparently formed from 6-methylphenanthridine by heating with acetic anhydride or benzoyl chloride, as can be judged from the characteristic change in the absorption spectra. However, these compounds have not yet been isolated.

EXPERIMENTAL

o-Methoxy-α-methylcinnamic acid was obtained in 50% yield by the method in [9].

o-Methoxy-α-methylcinnamic Acid 2-Diphenylylamide. A mixture of 3 g (15 mmole) of o-methoxy-α-methylcinnamic acid and 6.7 g (93 mmole) of freshly distilled thionyl chloride was refluxed for 1 h, after which the excess thionyl chloride was removed by vacuum distillation, 15 ml of xylene and 2.64 g (15 mmole) of 2-aminodiphenyl were added to the residue, and the mixture was refluxed until HCl evolution ceased. The xylene solution was washed with 5 M HCl, 15% Na_2CO_3, and water, and the xylene was removed by distillation. The residue was refluxed for 2 min in 25 ml of 5% NaOH, the mixture was cooled, and the precipitate was removed by filtration to give 1.5 g of the diphenylylamide with mp 90-91°. Crystallization from 50% alcohol (1 : 10) and petroleum ether (1 : 70) gave a product with mp 94-95° and R_f 0.52 (chloroform) and 0.15 (benzene).* IR spectrum in CCl_4: 3450 and 1680 cm^{-1}. PMR spectrum, δ, ppm ($CHCl_3$): 1.92 ($C-CH_3$), 3.68 (OCH_3). Found: C 80.7; H 6.6; N 3.8%. $C_{23}H_{21}NO$. Calculated: C 80.5; H 6.1; N 4.1%.

The diphenylylamide was heated at 130° for 4-5 h with phosphorus oxychloride (1.2 ml per gram) to give 3-methylcoumarin (60%) with mp 87-88° [10] and R_f 0.7 (chloroform). IR spectrum: ν_{CO} (CCl_4) 1730 cm^{-1}. PMR spectrum: δ_{CH_3} 2.02 ppm ($CHCl_3$). UV spectrum, λ_{max} (in alcohol), nm (log ε): 275 (4.07) and 307 (3.85).

6-(2-Phenyl-2-hydroxyethyl)phenanthridine (IV). A solution of 3.86 g (0.02 mole) of 6-methylphenanthridine in 20 ml of benzene was added to 25 ml of a solution of isopropylmagnesium bromide obtained from 0.48 g (0.02 g-atom) of magnesium and 2.68 g (0.02 mole) of isopropyl bromide in 20 ml of ether. Darkening of the mixture and gas evolution (propane) were observed. The solvents were removed by distillation, and the residue was heated at 80-85° for 1.5 h, at the end of which the mixture began to solidify. Ether (30 ml) was added to the solid mass, and the mixture was stirred with a glass rod. A solution of 2.12 g (0.02 mole) of benzaldehyde in 10 ml of ether was added, and the mixture was stirred and refluxed for 6 h. Saturated ammonium chloride solution (20 ml) was added, and the resulting precipitate was removed by filtration and washed with benzene and water. Two crystallizations from alcohol (1 : 15) gave 1.7 g of IV with mp 162° and R_f 0.15 (chloroform). IR spectrum: ν_{OH} 3270 cm^{-1} (in KBr). UV spectrum, λ_{max} in alcohol, nm (log ε): 250 (4.7), 272 (4.09),** 290 (3.88)**, 330 (3.50), 346 (3.50). Found: C 84.0; H 5.6; N 4.8%. $C_{21}H_{17}NO$. Calculated: C 84.3; H 5.7; N 4.7%.

*The R_f values presented were obtained with activity II Al_2O_3.

**Here and subsequently, the inflection points and shoulders are designated by two asterisks.

6-Styrylphenanthridine (VI). Concentrated sulfuric acid (2 ml) was added to a solution of 0.5 g (1.66 mmole) of IV in 8 ml of glacial acetic acid, and the mixture was heated rapidly to the boiling point and refluxed for 2-3 min. It was then poured into 15 ml of cold water, and the aqueous mixture was cooled and neutralized with 10% NaOH and extracted with benzene to isolate VI. The extract was dried with sodium sulfate, and the product was isolated as the picrate with mp 228° [3]. The base was isolated from the picrate and dissolved in benzene, and the solution was filtered through aluminum oxide. The benzene was removed by distillation, and the residue was crystallized from petroleum ether to give 0.4 g (86%) of VI as slightly yellowish needles with mp 134-135° (134° [3]) and R_f 0.9 (chloroform). IR spectrum: $\nu_{C=C}$ 1635 cm^{-1} (KBr). UV spectrum, λ_{max} (in alcohol), nm (log ε): 250 (4.51), 275 (4.38)**, 330 (4.21), 350 (4.20)**, UV spectrum in alcohol at pH 2, λ_{max}, nm (D): 250 (1.16), 332 (0.264), 380 (0.244).

6-[2-(o-Methoxyphenyl)-2-hydroxyethyl]phenanthridine (V). This compound, with mp 195° (from $CHCl_3$–petroleum ether), and R_f 0.2 (chloroform), was obtained in 25% yield by the method used to prepare IV. IR spectrum, cm^{-1} (KBr): 3350, 1240, and 1257 (broad, strong), UV spectrum, λ_{max} (in alcohol), nm (log ε): 250 (4.50), 273 (4.04)**, 295 (2.95)**, 330 (3.37), and 338 (3.33). Found: N 4.3%. $C_{22}H_{19}NO_2$. Calculated: N 4.3%.

6-(o-Methoxystyryl)phenanthridine (VII). This compound, with mp 114-115° [from petroleum ether (1 : 15)], was obtained in 67% yield by the method used to prepare VI. IR spectrum, cm^{-1} (in KBr): 1627 and 1253. UV spectrum, λ_{max} (in alcohol), nm (log ε): 250 (4.63), 282 (4.41)**, and 330 (4.24). Found: N 4.3%. $C_{22}H_{17}NO$. Calculated: N 4.5%.

6-(p-Methoxystyryl)phenanthridine. A mixture of 0.98 g (5 mmole) of 6-methylphenanthridine, 0.68 g (5 mmole) of p-methoxybenzaldehyde, and 0.68 g (5 mmole) of anhydrous zinc chloride was heated at 150-160° for 4 h, after which the styryl was extracted from the melt with chloroform. The chloroform was removed from the extract by distillation, and the residue was dissolved in 50 ml of benzene. The solution was filtered through aluminum oxide, and the filtrate was evaporated. The residue was crystallized from a tenfold amount of alcohol–benzene (2 : 1) to give 0.7 g of light-yellow crystals with mp 140-141°. PMR spectrum: δ 3.8 ppm ($CHCl_3$). UV spectrum, λ_{max} (in alcohol), nm (log ε): 250 (4.65), 275 (4.35)**, and 360 (4.35). UV spectrum in alcohol at pH 1, λ_{max}, nm (D): 250 (1.12), 260 (1.0)** 330 (0.26), and 410 (0.23). Found: C 84.8; H 5.9; N 4.6%. $C_{22}H_{17}NO$. Calculated: C 84.8; H 5.5; N 4.5%. An identical compound was obtained in lower yield by refluxing equimolecular amounts of methylphenanthridine and anisaldehyde in a 20-fold quantity of acetic anhydride for 20 h.

6-(p-Nitrostyryl)phenanthridine. A 0.3-g (1.5 mmole) sample of 6-methylphenanthridine and 0.23 g (1.5 mmole) of p-nitrobenzaldehyde were refluxed in 9 ml of acetic anhydride for 12 h, and the resulting crystals were removed by filtration and washed with acetic anhydride and petroleum ether to give 0.4 g (81.5%) of the styryl. It was dissolved in 40 ml of chloroform, and the solution was washed with 15 ml of 5% NaOH and water and dried with Na_2SO_4. The solution was then treated with activated charcoal and evaporated to one third of its original volume to give 0.18 g of bright-yellow crystals with mp 233-234°. The product was only very slightly soluble in hot alcohol (1 : 1000) and had R_f 0.55. (benzene). UV spectrum, λ_{max} (in alcohol), nm (log ε): 246 (4.55), 255 (4.47)**, 295 (4.25), and 368 (4.39). UV spectrum in alcohol at pH 1, λ_{max}, nm (D): 248 (1.00), 330 (0.62), and 390 (0.49). Found: C 77.8; H 4.7; N 8.5%. $C_{21}H_{14}N_2O$. Calculated: C 77.3; H 4.3; N 8.6%.

6-Cyanomethylphenanthridine (X). This compound, with mp 107-108° from alcohol (1 : 5) and petroleum ether (1 : 25) and R_f 0.6 ($CHCl_3$), was obtained in 52% yield by the method in [11]. IR spectrum: ν_{CN} 2240 cm^{-1} (in KBr). UV spectrum, λ_{max} (in alcohol), nm (log ε): 250 (5.1), 270 (4.74)**, 290 (4.57)**, 330 (3.97), and 350 (3.97).

6-(α-Cyanostyryl)phenanthridine (XI). A solution of sodium ethoxide from 0.04 g of Na and 2 ml of ethanol was added with stirring to a solution of 0.4 g (2 mmole) of X and 0.21 g (2 mmole) of benzaldehyde in 18 ml of ethanol, and the mixture was refluxed for 2 h. It was then cooled, and the resulting precipitate was removed by filtration. Crystallization from alcohol (1 : 10) gave 0.38 g (62%) of the styryl with mp 201° and R_f 0.85 [hexane–ether (1 : 1)]. IR spectrum (in KBr), cm^{-1}: 2195, 1620, 1565, 1487, 1463, 1450, 1365, 1325, 1215, 1195, 1175, 965, 925, 860, 755, 735, 720, and 675. UV spectrum, λ_{max} (in alcohol), nm (log ε): 248 (4.50), and 270-290 (4.3; a broad shoulder that decreases slopingly to 320 nm and then sharply to 380 nm). Found: C 86.5; H 4.4; N 9.2%. $C_{22}H_{14}N_2$. Calculated: C 86.2; H 4.6; N 9.2%.

5-Acetyl-6-cyanomethylene-5,6-dihydrophenanthridine (XIII). A 0.2-g sample of X was refluxed in 6 ml of acetic anhydride for 4 h, after which the mixture was cooled and filtered to give 0.15 g of XIII. The

product was crystallized from benzene (1:40) to give yellow needles with mp 214-215°. PMR spectrum in $CDCl_3$, δ: 2.55 ppm ($COCH_3$, singlet). IR spectrum, cm^{-1} (KBr): 2180, 1630, 1600, 1585, 1530, 1500, 1480, 1405, 1360, 1225, 1170, 1140, 985, 935, 765, 750, and 710. UV spectrum, λ_{max} (in alcohol), nm (log ε): 241 (4.54), 255 (4.32)**, 272 (4.18), 293 (3.95), 320 (3.70), 335 (3.70), 370 (4.00)**, 387 (4.29), and 408 (4.32). Found: C 78.7; H 4.9; N 11.1%; M 273 (with a Hewlett Packard 302 Bosmometer, in chloroform). $C_{17}H_{12}N_2O$. Calculated: C 78.5; H 4.6; N 10.8%; M 260. For hydrolysis, 0.1 g of XIII was heated with 6 ml of 30% H_2SO_4 at 140° for 8 h, after which the mixture was neutralized and extracted with benzene to give 0.06 g (84%) of 6-methylphenanthridine with mp 81-82°, which was identical to a genuine sample.

6-(p-Dimethylamino-α-cyanostyryl)phenanthridine (XII). A) A 3-g (15 mmole) sample of X and 2.3 g (15 mmole) of p-dimethylaminobenzaldehyde were refluxed in 80 ml of acetic anhydride for 8 h, after which the mixture was cooled and filtered to give 1.3 g of XIII. The filtrate was vacuum evaporated to 20 ml, cooled, and filtered to give 1.2 g of XII with mp 182°. Crystallization from benzene (1:15) gave 0.65 g of styryl XII with mp 189° and R_f 0.65 [hexane–ether (1:1)] and 0.5 [acetone–hexane (1:1)]. IR spectrum, cm^{-1} (in KBr): 2190, 1615, 1590, 1580, 1565, 1380, 1365, 1195, 1170, 965, 820, 760, and 725. UV spectrum, λ_{max} (in alcohol), nm (log ε): 247 (4.68), 298 (3.96), 307 (3.96) and 408 (4.50). UV spectrum in alcohol at pH 1, λ_{max}, nm (log ε) 245 (4.59), 270 (4.24)**, 385 (4.07), 400-406 (3.94)**, and 516 (4.24). UV spectrum in a strongly acidic alcohol solution, λ_{max}, nm (D): 250 (1.40), 270 (0.48)**, 335 (0.367), 385 (0.178), and 409 (0.125). Found: C 82.5; H 5.7; N 11.8%. $C_{24}H_{19}N_3$. Calculated: C 82.5; H 5.5; N 12.0%.

B) This compound, with mp 183-184° (from benzene–petroleum ether), was obtained in 43% yield by the method used to prepare XI.

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